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Creutzfeldt-Jakob disease-like periodic sharp wave complexes in voltage-gated potassium channel-complex antibodies encephalitis : A Case Report

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Abstract

Introduction—Voltage-gated potassium channel-complex antibodies (VGKC-cAbs) encephalitis, a treatable autoantibody encephalopathy, has been previously reported to clinically mimic sporadic Creutzfeldt-Jacob disease (sCJD). Among available clinical clues to distinguish them, periodic sharp wave complexes (PSWC), a typical finding in sCJD, have never been reported in association with VGKC-cAbs encephalitis.

Case presentation—A 76 years old man was transferred to a tertiary neurology center with a clinical history of six-month weight loss, cognitive disturbance and non specific generalized weakness. He had two seizures the month before transfer and then evolved to severe encephalopathy, requiring mechanical ventilation. PSWC every 1–2 seconds over slowed background were found on EEG, and MRI showed cerebellar and bifrontal cortical T2/FLAIR/DWI hypersignal without restricted diffusion on ADC mapping. Pancorporeal PET-scan was negative. An immunotherapy trial did not improve the patient condition. Therefore, he died after life support withdrawal. Brain autopsy revealed mononuclear neocortex infiltrate without significant spongiosis, and the anti-VGKC test showed a seropositivity of 336 pmol/L (normal: 0–31), three month after the patient deceased.

Conclusion—This is the first reported case of VGKC-cAbs encephalitis associated with PSWC on EEG, which further confuse the differential diagnosis with sCJD. However, the cortical DWI

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Conflicts of Interest :

Dr Martin Savard, Annie Guillemette, Stéphanie Gosselin-Lefebvre, Gerard H. Jansen, Peter V. Gould and Robert Laforce Jr report no conflict of interest.

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hypersignal without restriction seem to remain a way to discriminate these two entities appropriately, when present. These clues are of paramount importance since VGKC-cAbs encephalitis is a treatable disease.

Keywords

Auto-immune encephalitis; Creutzfeldt-Jacob disease; Voltage-gated potassium channel-complex antibodies encephalitis; EEG; Periodic sharp waves complexes; MRI

Introduction

Voltage-gated potassium channel-complex antibodies (VGKC-cAbs) cause a broad spectrum of neurological conditions including acquired neuromyotonia, Morvan syndrome, limbic encephalitis and epilepsy (Tan et al., 2008). Of particular interest, VGKC-cAbs in association with cognitive impairment has now been reported in more than 400 cases, many of whom often showed remarkable reversibility of symptoms with immunotherapy when compared to cases with many forms of paraneoplastic encephalitis or sporadic Creutzfeldt-Jacob disease (sCJD), emphasizing the importance of prompt recognition (Thieben et al., 2004; Vincent et al., 2004; Korth et al., 2006; Irani & Peters, 2010).

One series specifically described cases with VGKC-cAbs which mimicked sCJD (Geschwind et al., 2008). Clinical features which differentiated the two conditions included serum hyponatremia in patients with VGKC-cAbs and the characteristic MRI changes of sCJD. To our knowledge, no patient with VGKC-cAbs has been reported to have electroencephalographic periodic sharp wave complexes (PSWC). We report herein a patient with VGKC-cAbs and consistent pathology, whose clinical picture and EEG features mimicked sCJD.

Case Presentation

A 76 year-old man, with previous medical history of type 2 diabetes, was transferred to the intensive care unit of a tertiary neurological center to perform continuous EEG monitoring. During the previous six months, he had significant weight loss (40 pounds) along with cognitive decline (apathy, decreased attention and aggressiveness) and proximal weakness. He reportedly had difficulty walking straight and would sometimes hold on to walls around him without dizziness. One month before admission to our center, he presented to another hospital with two generalized tonic-clonic seizures. On that admission, basic blood tests, HIV, antithyroid antibodies, and two lumbar punctures were normal. No hyponatremia was noted. Serum VGKC-cAbs were sent. In light of his proximal weakness and decreased deep tendon reflexes despite a normal EMG, he was given an aggressive immunotherapy treatment, including intravenous immunoglobulin (2g/kg divided on 5 days), and 3 weeks later steroids (solumedrol 1g IV id for 5 days) combined with plasma exchange without any improvement. He progressed to akinetic mutism and later required mechanical ventilation. On the day he was transferred to our center, myoclonus involving face, arms and trunk were first observed: these were of shorter duration and less frequent than faciobrachial dystonic seizures.

Upon arrival at our center, he could open his eyes in reaction to pain, but showed no eye contact or clear response to simple commands. Cranial nerves examination was otherwise normal other than hyporeflexia. Brain MRI showed (Figure 1 A–F) cortical hyperintensity on FLAIR/T2/DWI sequences, mainly in the cerebellum, left hippocampal uncus, right parahippocampal gyrus and bilateral medial frontal (anterior cingulate) regions. Basal ganglia were spared. The differential diagnosis considered by the neuroradiologist was atypical herpes encephalitis, sCJD or limbic encephalitis. Continuous EEG-monitoring (Figure 2) showed PSWC every 1–2 seconds, increased sometime by stimulation (therefore qualifying sometime as SIRPIDs), and with an anterior predominance over a slowed background. No myoclonus was observed during recording. A body PET-scan was negative for neoplasia.

Considering his age and unfavourable clinical evolution in spite of previous aggressive immunotherapy, the medical team, in accord with family wishes, ceased life-sustaining therapies five weeks after his first hospital admission. He died in palliative care three days after mechanical ventilation withdrawal. Autopsy of the brain conducted by the Canadian Creutzfeldt-Jakob Disease Neuropathology Laboratory in Ottawa (Ontario) showed arachnoid and white matter perivenular mononuclear infiltrates, with increase in neocortical microglial cells (CD68) but no significant spongiosis (Figure 1 G–I). None of the characteristic abnormalities for a prionosis were found (no typical vacuolation, nor prion protein deposition in the 12F10 prion protein antibody stain), hence ruling out prion disease. Findings of mononuclear infiltrates in arachnoid, neocortex, especially in the cerebellum were highly suggestive of auto-immune encephalitis (Bien et al., 2012). Three months after death, VGKC-cAbs results were reported as elevated at 336 pmol/L (normal range: 0–31) by radioimmunoassay, confirming the diagnosis of VGKC-cAbs encephalitis.

Discussion

Striking similarities between VGKC-cAbs encephalitis and sCJD have been noted as they both often present with subacute cognitive impairment, apraxia, ataxia, myoclonus, parkinsonism and diffuse EEG slowing (Geschwind et al., 2008; Tan et al., 2008). The major difference between these two entities remains their clinical evolution: patients with VGKC-cAbs encephalitis often show significant improvement (50% to 89%) with immunomodulatory therapy whereas patients with CJD always have a fatal outcome (Thieben et al, 2004; Vincent et al, 2004; Tan et al, 2008). Therefore, the clinical syndrome and antibody testing should be considered early in such presentations, yet limited availability of VGKC-cAbs testing, or as in our case prolonged reporting of results, might not permit definitive diagnosis and treatment in a timely fashion. Among clues used to distinguish these diseases, the presence of hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) occurs rarely in sCJD (Ishida et al., 2003), but is reported in 36% to 80% of VGKC-cAbs encephalitis (Vincent et al., 2004; Geschwind et al., 2008; Tan et al., 2008); this was absent in our case. The presence of neoplasia (seen in between 5 and 30% of patients with VGKC-cAbs encephalitis) (Vincent et al., 2004; Tan et al., 2008) sometimes helps, but here again was absent. Faciobrachial dystonic seizures, not noted in our patient, also appear specific for VGKC-cAbs encephalitis (Irani et al., 2011). One of us (MDG) has previously reported an in-depth review of 15

patients sharing common clinical manifestations with sCJD but proven to be seropositive for VGKC-cAbs, with even 60% of them satisfying the World Health Organization symptom criteria for probable sCJD (Geschwind et al., 2008). MRI DWI cortical hyperintensities with absence of restricted diffusion on ADC mapping were reported in two patients (Geschwind et al., 2008), as in our case. Even if the absence of restricted diffusion was atypical for sCJD (Vitali et al., 2011), these MRIs were judged by neuroradiologists to be possibly consistent with sCJD. None of the 15 VGKC-cAbs had PSWCs in that series, although EEG was abnormal (slowing) in 9 of 13 patients (Geschwind et al., 2008). Otherwise, two previous series of patients with VGKC-cAbs encephalitis not necessarily sharing the clinical characteristics of sCJD showed that 80–85% of patients had an abnormal EEG, typically with diffuse slowing (Vincent et al., 2004; Tan et al., 2008), but two cases had generalized triphasic waves, with no mention if they were periodic (Tan et al., 2008).

PSWCs are reported to occur during EEG recording in about two thirds of patients with sporadic CJD (Levy et al., 1986; Steinhoff et al., 2004). They typically consist of either simple sharp waves (including biphasic and triphasic waves) or complexes with mixed spikes, polyspikes and slower waves with a typical duration of 100–600 msec having a fronto-precentral maximum, recurring every 0.5–2 seconds with intervening background consisting of generalized low voltage slowing (Wieser et al., 2006). In comparison, triphasic waves by themselves are positive sharp transients waves that are preceded and followed by negative waves of relatively lower amplitude, often but not always being periodic compared to PSWC. The clinical association of toxic, metabolic or anoxic factors as an etiologic explanation for the encephalopathy, none being present in our case, is also important to consider in the presence of triphasic waves (Wieser et al., 2006). Interestingly, it has been suggested in the past that triphasic waves may have a source located in the medial frontal area, which was one of the main region involved in our patient according to the MRI (Kwon et al., 2007). In a study of 214 definite sCJD cases and 77 definite non-CJD cases in which EEG, cerebrospinal fluid 14-3-3 protein and MRI were compared, PSWCs were found to have the lowest sensitivity (44%) but the highest specificity (92%) to diagnose sCJD (Zerr et al., 2009). Given that specificity, with all the prognosis implications associated with such an EEG finding, a thorough comprehension of the associated differential diagnosis of PSWC is of paramount importance. Likewise, other previously reported diagnosis that could generate PSWC are Alzheimer disease, vascular dementia and Lewy body disease (Wieser et al., 2006).

Conclusion

This case emphasizes that, despite its high reported specificity for sCJD, PSWCs on EEG-monitoring may be associated with VGKC-cAbs encephalitis, even in patients with diffuse DWI cortical changes evoking sporadic CJD. The lack of restriction on diffusion imaging in VGKC-cAbs encephalitis might prove more specific to differentiate these two diseases (Vitali et al., 2011). This clinical differentiation is of great importance given the potential reversibility of VGKC-cAbs encephalitis with immunotherapy compared to the always fatal evolution of CJD. Our patient died despite aggressive immunotherapy, again emphasizing the severity of this condition, and the need for early diagnosis. In a critical care context like

the one described here, obtaining a VGKC-cAbs assay in a timely fashion and focusing on specific imaging rather than EEG signs might have a significant impact on patient outcome.

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Figure 1.

(A) Brain axial magnetic resonance images in FLAIR showing bifrontal, left > right anterior cingulate, cortical ribboning. (B) Same finding on DWI. (C) ADC mapping showing however the absence of restriction. (D, E, F) Same finding at the cerebellum, mainly on left, respectively on FLAIR, DWI and ADC map again. The lack of restricted diffusion suggests against CJD. (G, H, I) Neuropathologic examination of the cerebellar vermis at autopsy, respectively with HPS stain (I) and CD69 antibody (J), shows focal increase in cortical

microglial cells, but no significant spongiosis. (K) Immunohistochemical screening for PrP^{Sc} deposits with 12F10 antibody shows no evidence of prions.

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Figure 2.
EEG showing periodic sharp wave complexes on a longitudinal bipolar montage, waves having either a biphasic or triphasic morphology.